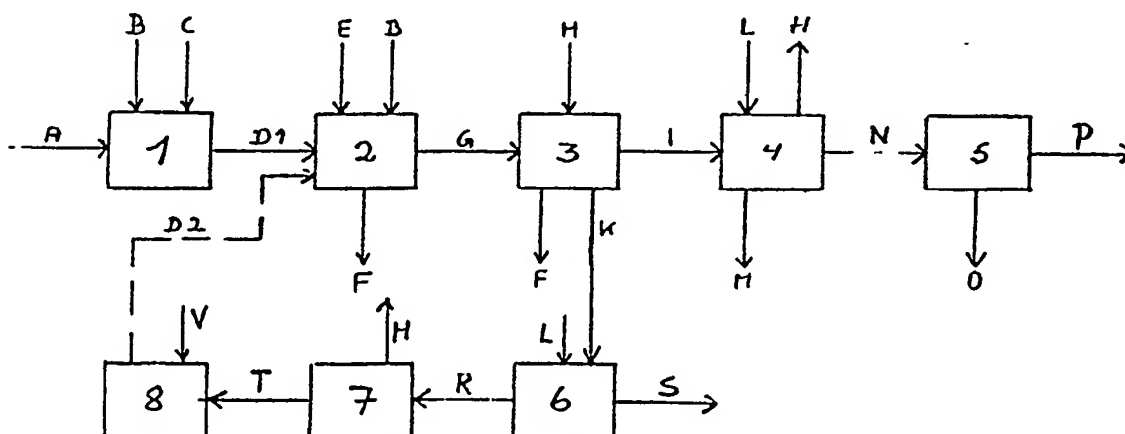




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: A REFINED FISH OIL CONCENTRATE AND THE PRODUCTION PROCESS FOR SAMPLE



## (57) Abstract

Refining of fish waste product so that a concentrate of  $\omega$ 3-fatty acid alkyl ester is formed with 20-30% eicosapentaenoic acid alkyl ester and 35-50% docosahexaenoic acid alkyl ester (both by weight) free from cholesterol. The  $\omega$ 3-concentrate is produced through urea precipitation of the non- $\omega$ 3-fatty acid esters so that the filtrate from the precipitation may be extracted by means of hexane for the transmission of the  $\omega$ 3-fatty acid esters and the cholesterol to the hexane extract. Hexane is thereafter removed. The remaining concentrate of the fatty acid esters with the cholesterol is cooled to a temperature of not lower than  $-50^{\circ}\text{C}$ , whereby the cholesterol is crystallized. The remainder is a  $\omega$ 3-concentrate with the composition mentioned above.

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A refined fish oil concentrate and the production process for same.

The present invention concerns a refined fish oil concentrate as well as the production process for same. In the refining process, cholesterol and useful biproducts such as urea adducts of fatty acid compounds are produced, in addition to higher unsaturated fatty acids.

It is known that waste products from the fish refining industry contain usable products, among others fatty acids, cholesterol, proteins and enzymes. These are either fat-soluble or water-soluble. Such waste products are normally referred to as fish entrails.

Through the processing of fish entrails, the water-soluble portion containing proteins and enzymes may be separated from the fat-soluble portion. The present invention concerns only the fat-soluble portion of the waste products, but it can also be used for other refined fish oils such as occur for instance in the fish product industry. In the following this will be called fish oil product.

It is known that certain essential fatty acids in fish oil have a medicinal effect and are used in the prevention and cure of thrombotic illnesses, for instance ischemic heart disease. In addition, these compounds lower the cholesterol level in the blood.

Among the above-mentioned fatty acids, the following may be specified as suitable for the medicinal purpose referred to: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Both fatty acids are  $\omega$  3-fatty acids of the C-20 and C-22 acids. Their nomenclature according to the IUPAC system is:

for the eicosapentaenoic acid (EDA)

cis - 5, 8, 11, 14, 17 - eicosapentaenoic acid and for the docosahexaenoic acid (DHA)

cis - 4, 7, 10, 13, 16, 19 - docosahexaenoic acid

which is abbreviated to:

eicosapentaenoic acid 20:5  $\omega$  3 and

docosahexaenoic acid 22:6  $\omega$  3

where 20 and 22 indicate the number of C-atoms in the molecule of fatty acid, 5 and 6 the number of unsaturated bondings, and  $\omega$  3 that the last unsaturated bonding is positioned in a distance of 3 carbon atoms from the  $\omega$ -position.

In the following we will be using the description EPA and 20:5  $\omega$  3 for the eicosapentaenoic acid and DHA and 22:6  $\omega$  3 for the docosahexaenoic acid.

The fat soluble portion of cod entrails usually contains 10 - 25% of the essential fatty acid compounds EPA and DHA, as well as 2 - 4% cholesterol. The remainder is mainly fatty acid compounds with lower unsaturation, such as pure fatty acids or their glycerides.

The purpose of the invention is to separate the essential fatty acid compounds from cholesterol and the remaining fatty acid compounds.

Another purpose of the invention is to produce from a non-uniform raw material containing marine fatty acids and/or esters of these fatty acids, as well as cholesterol as main

components after trans-esterification with a lower alcohol, and under alkaline conditions produce a concentrate containing the essential  $\omega$ 3-fatty acid compounds, EPA and DHA, as well as isolate the cholesterol and the urea adduct of the saturated and lower unsaturated fatty acid compounds, which then appear in their own product fractions.

It has long been known that the easiest way to separate fatty acids is by means of extraction or distillation when they appear in the form of esters, for instance as methyl or ethyl esters. Before treatment, fatty waste products from the fish industry must have been subjected to trans-esterification and esterification, for instance with methanol for production of fatty acid methyl esters.

This basic material is well suited for further separation of essential fatty acid compounds and cholesterol from the remaining less important fatty acid compounds.

In US Patent Publication No. 4.145.446 a method is described for precipitation of fatty acid compounds in raw material by means of urea. The purpose is to obtain a product containing proteins and fats, suitable for fodder. The production of the urea adduct is brought about by having a solution of melted urea at 60 - 140° C to which is added melted fatty acid or a mixture of fats heated to a temperature of 35-105° so that the ratio fat/fatty acids to urea will be from 40/60 to 60/40 units by weight.

Another patent, SU 950.393 describes a method for production of cholesterol from for instance fish waste products by hydrolysing the fatty acid compounds and converting them to soaps. These are then subjected to an extraction of trichloroethylene at room temperature, whereby the cholesterol is combined with the trichloroethylene and this compound is then subject to further separation.

GB 1.240.513 also concerns a separation technique by means of urea where the raw material consists of pure methyl and ethyl esters of the  $C_{16}$ - $C_{18}$  fatty acids. Urea precipitation occurs in a neutral environment with a surplus of the relevant alcohol. The purpose is to be able to obtain a stronger concentration of the  $\gamma$ -linolenic acid. The above-mentioned fatty acid esters do not contain any higher fatty acids other than C-18 in the form of stearic acid, oleic acid, linoleic acid and linolenic acid, which after the urea precipitation and separation of the urea adduct from the rest of the material has obtained a higher content of  $\gamma$ -linolenic acid by means chromatography.

The higher unsaturated fatty acid compounds 20:5  $\omega$ 3 and 22:6  $\omega$ 3 may be concentrated according to a method described in J 59-071396 where the fatty acid compounds mentioned are extracted by means of polar solvents, such as acetone, methyl ethyl ketone, methanol, ethanol, and similar solvents, whereby a soluble and an insoluble extract are formed. Thereafter the extract is further processed to obtain essential fatty acid compounds.

According to the invention it now appears possible - in a remarkably simple manner - to optimize the procedure to increase the concentration of  $\omega$ 3-fatty acid compounds and cholesterol by means of a simplified process. This is based on a fractionated precipitation of the less interesting fatty acid compounds with urea, since urea tends to form an adduct with fatty acids which do not belong to the  $\omega$ 3 type. Nor does cholesterol form an adduct with urea. The procedure used previously was to isolate the fatty acid compounds before these were esterified separately, and then they were subjected to a fractionated precipitation with urea. This procedure is unnecessary with our invention.

A special feature of this process is that fatty acid compounds are not produced prior to precipitation of urea, but precipitate from the same non-uniform mixture of components like they are found in the raw material.

Another special feature is that the precipitation of urea takes place in an alkaline environment, and in such a way that the alkaline environment is created through applying the base only in catalytic quantities such as a catalytic agent for the trans-esterification of glycerides to methyl esters and not as a means of saponification of the fatty acids.

A third special feature is that the trans-esterification takes place at room temperature.

A result of trans-esterification at low temperature and in an environment with low alkalinity is that isomerization of the double compounds is avoided, which results in a more uniform product with no toxic effect. At the same time transcon-figurations are avoided. The remaining solution is thereafter extracted by means of non-polar solvents, among others hexane, whereby the  $\omega$ 3-fatty acids as well as cholesterol will be found in the hexane phase.

Thereafter the non-polar phase is subjected to evaporation of the hexane under moderate conditions, for instance by means of vacuum distillation. The remaining  $\omega$ 3-concentrate now contains all the cholesterol, and it becomes apparent that the cholesterol does not dissolve easily in this concentrate and may crystallize in cooling. The  $\omega$ 3-concentrate which is left will - according to the simplified process invented - contain 20 - 30 per cent EPA by weight and 35-50% DHA by weight. The rest consists mainly of non-essential fatty acid compounds and are not important for our purpose.

For a better understanding of the invention, we refer to the block diagram in Fig. 1, where each block represents a step in the process and is marked with a reference number. The flow of the material to and from each block and between the blocks is marked by solid and dotted lines. In addition, each material is characterized by a letter.

The basic material is fat and/or fatty acids from fish and especially fat and/or fatty acids obtained from the fish processing industry in connection with ensilage and or autocatalysis processes, but the process may also be used for other forms of marine fat. This fatty raw material is called a fish oil product in the claims.

Such fat/fatty acids have a high content of saturated, unsaturated and polyunsaturated fatty acids with a chain length C 18, C 20 and C 22 as well as a certain amount of cholesterol, vitamins and other fat soluble products which are undefinable, usually characterized as unsaponifiable, as well as fatty acid compounds with shorter chain lengths.

#### Box 1.

Fat/fatty acids (A) from fish with a content of i.a. cholesterol, also called the fish oil product, was placed in a container for trans-esterification with an alcohol with a low boiling point (B), for instance methanol or ethanol, preferably methanol, and a catalytic agent as well as auxiliary compounds (C) to obtain a faster esterification and trans-esterification in order to prevent oxydization and discoloration. Potassium hydroxide may be used as a catalytic agent and in order to prevent oxidization, especially when heavy metals are present, such as chromium, iron, cobalt, nickel and copper, small amounts of the sodium salt of ethylenediaminetetra-acetic acid (EDTA- $\text{Na}_3$ ) may be added. The esterification and trans-esterification take place under moderate conditions and stirring at about 20° C for some

hours. The formation of alkyl esters is nearly complete when the ester product has changed its appearance from opalescent to clear. The clear solution (D1) therefore contains alkyl esters of the fatty acids, glycerol, alkanol, as well as some water from the esterification of the free fatty acids.

Box 2.

The clear solution is then heated to a temperature of 65-68°C, whereafter a fixed amount of urea (E) and alkanol (B) is added and stirred in until everything is completely dissolved. The amount of urea depends on the composition of the fatty acids so that if the raw material (A) contains 6-8% EPA by weight, urea is added in the ratio 3 parts urea by weight to 1 part alkyl ester. In order to ensure that the components are completely soluble, 9 parts alkanol by weight is added.

When everything is dissolved, the solution is slowly cooled to approx. 20° C. An adduct of urea fatty ester (F) is crystallized and then removed by means of for instance decanting and filtration, whereafter the filter mass is cooled to 0° C in order to crystallize a larger portion of the adduct (F). The adduct is then separated by a known method so that the remaining filter mass (G) contains the essential fatty acid fractions and the unsaponifiable fractions.

Box 3.

The slightly alkaline filter mass (G) is saturated with hexane and is extracted by means of this solvent through a known technique as for instance by a continuing fluid-to-fluid counter current process, whereafter a further quantity of adduct of urea fatty ester may be crystallized. By means of this extraction two fluids are formed, consisting of hexane (I) and a residue (K).

## Box 4.

The hexane extract (I), which contains the alkyl-fatty esters of the polyunsaturated fatty acids 18:4  $\omega$ 3, 20:5  $\omega$ 3 and 22:6  $\omega$ 3 as well as cholesterol as the most important components, is washed in a diluted hydrochloric acid (L) in order to neutralize possible potassium soaps of the essential polyunsaturated fatty acids in the hexane extract. The washing water is decanted.

Hexane (H) is thereafter removed by evaporation of the extract (I) so that a concentrate is produced which is free from solvents (N) and which contains the compounds that are essential for the invention, the fatty acid compounds EPA and DHA as well as cholesterol.

The dehydrated extract normally contains 20-30 % EPA, 35-45% DHA, 10-20% other polyunsaturated fatty acids, as well as 5-15% cholesterol and undefined compounds, all by weight, but the composition referred to will depend on the type of fish used, the time of year the fish is caught, and the type and condition of the raw material.

## Box 5.

The concentrate of alkyl fatty acid ester (N) is thereafter cooled to approx. minus 25° C, whereafter cholesterol (O) is crystallized. This is centrifuged/filtered.

Further impurities which are present in the concentrate (N) may be removed by cooling the mixture to a temperature of lower than minus 25° C, whereafter certain undefined compounds are precipitated and filtered by means of a known method. The remaining  $\omega$ 3-concentrate (P) thus contains 20-35% EPA, 35-50% DHA and 15-25% of other polyunsaturated  $\omega$ 3-fatty acid compounds (all by weight) as well as unsaturated fatty acid compounds which are not essential for the invention.

Product (P) which contains the alkyl esters of the corresponding  $\omega$ 3-fatty acids may be utilized as it is or the concentration of EPA and DHA may be increased.

Since the product contains only small amounts of other fatty acids with the same chain length as EPA and DHA, it is well suited for separation of the essential fatty acids, EPA and DHA by means of supercritical fluid extraction.

Another method for increasing the concentration is by means of preparative liquid chromatography by which method a more than 90% purity of the essential fatty acids is obtained.

Box 6.

The alkaline residue (K) is acidified by means of concentrated hydrochloric acid (L) to a pH = 2, whereafter a hexane fraction (R) is precipitated in an upper layer which is separated. One may also subject the acid solution (S) to further extraction by means of hexane if this should be necessary, whereafter the hexane extracts are gathered. The hexane fractions (R) contain free fatty acids as well as some of their alkyl esters and fairly high percentages of EPA and DHA, but also a fairly substantial portion of C 18-, C 20- and C 22-fatty acids with lower unsaturation. This acid solution contains water, alcohol, alkanol, glycerol, urea and other products which may be retrieved by a separate process which is not described here.

Box 7.

The fatty acid components of the hexane fraction are increased by evaporating hexane (H) in a separate piece of equipment.

Box 8.

The remaining solution is esterified using lower alkanols, for instance methanol or ethanol by means of an appropriate

catalytic agent (V) which for instance may be dehydrated hydrochloric acid, acetic acid chloride or boron-trichloride.

The resultant alkyl ester (D2) from the fatty acid components (T) from box 7 may be processed in various ways, for instance returned to box 2 for urea precipitation of the less unsaturated fatty acids.

#### Example

To 50 kg fish oil product (A) from cod entrails (containing 8% EPA, 11% DHA, and 2.3 % cholesterol all by weight) 400 l methanol (B) and 10 g EDTA Na<sub>3</sub> (C) were added in a reactor. Potassium hydroxide (C) dissolved in methanol was added for neutralisation of free fatty acids in a quantity corresponding to a colour reaction of pH 12 on a moist pH-paper. Thereafter 50 l methanol (B) were added.

The whole mixture was subjected to stirring for 15 hours at 20°C in order to bring about a trans-esterification of the glycerides to methyl esters and esterification of the free fatty acids to methyl esters.

When the trans-esterification was complete, the temperature was increased to 65 - 68° C and 140 kg urea (E), as well as a fixed amount of methanol (B) were stirred in while being heated until everything seemed to be dissolved.

Then the solution was slowly cooled to room temperature (approx. 20°C), whereafter a urea adduct of fatty acid was precipitated (F). It contained the major portion of the saturated and lower unsaturated fatty acid methyl esters.

The urea adduct was separated from the solution by decanting and filtering according to an ordinary, known technique.

Result: 100.1 kg urea adduct (F).

Thereafter the solution was cooled to 0 - 4° C, whereby an additional 5.1 kg urea adduct (F) could be filtrated from the solution.

This filtrate (G) contained  $\omega$ 3-polyunsaturated fatty acid methyl esters, cholesterol and a residue of unwanted fatty acid fractions with lower unsaturated C 18, C 20 and C 22 fatty acid methyl esters. To this filtrate we added hexane for saturation, whereby a further amount of urea adduct (22 kg) could be separated. This hexane-saturated solution was extracted in a counter-current with hexane so that the hexane extract (I) finally made up approx. 300 l. The remaining unextracted solution is called (K). The hexane extract was thereafter evaporated. The yield of  $\omega$ 3-fatty acid methyl ester concentrate : 10.2 kilos.

The concentrate (N) which contained 23% EPA , 41% DHA and 8% cholesterol, all by weight, was thereafter cooled to minus 25°C, whereby pure cholesterol (O) crystallized and was removed by means of centrifuging during which time the residue in the centrifuge was washed with hexane with a lower temperature in order to remove the fatty acid methyl esters from the cholesterol crystals. Yield: 760 g pure cholesterol. The concentrated filtrate (P) contained 25% EPA-methylester, 43% DHA-methylester by weight based on the fatty acid portion and traces of cholesterol.

The above-mentioned extracted residue (K) was cleansed with a solution of concentrated hydrochloric acid, whereby one hexane phase could be filtered off. Additional hexane was added to the batch, stirred and then precipitated. The hexane fractions were put together and the hexane evaporated. To 7.7 kilos of the remaining fatty acid and the methyl fatty acid fraction , 15 liter 2% methanolic solution of boron trichloride was added.

Yield: 6 kilos methyl fatty acid esters, containing 13% EPA-metylester, 17% DHA-metylester and approximately 2% cholesterol, all by weight.

The methyl fatty acid concentrate, containing methanol, was returned to the process for treatment with urea.

With this invention it has been possible to produce a very pure  $\omega$ 3-concentrate of fatty acid alkyle esters, where the essential anti-thrombotic fatty acid components eicosa-pentaenoic acid (EPA) and docosahexaenoic acid (DHA) is present in a strong concentration

Further, by means of the procedure invented, it has been possible in a simple manner to separate very pure and crystalline cholesterol. An additional product is a urea adduct of fatty acid components, but this is of no interest to the invention.

Another advantage with the invention is that it is possible to produce a urea adduct based on the same procedure where a trans-esterification has been done from glycerides to alkanol esters without following the cumbersome procedure by first producing the fatty acids, esterify these with alkanol and then separate them by means of the fractionated urea precipitation.

By following the procedure invented, it is also possible to avoid the formation of emulsions in the phases, and the phase separation is thereby facilitated during later extraction stages.

Claims

1. A refined fish oil concentrate, containing alkyl esters of  $\omega$ -3 eicosapentaenoic and docosaheptaenoic acid,  
c h a r a c t e r i z e d i n t h a t  
the concentrate at least make up 25% eicosapentaenoic acid and 35% docosaheptaenoic acid by weight, based on the fatty acid portion and that the refined fish oil concentrate also contains a rest which among other things consists of other unsaturated fatty acid compounds and that the fatty acid compounds are mainly present as alkyl esters of lower alcohols.
2. A refined fish oil concentrate according to claim 1,  
c h a r a c t e r i s e d i n t h a t  
said alkyl esters preferably are methyl esters of the fatty acids.
3. Process for the production of a refined fish oil concentrate, according to claims 1 and 2,  
c h a r a c t e r i z e d i n t h a t  
the fat/fatty acid fraction of the fish oil product is esterified and/or trans-esterified at room temperature with a lower alcohol in an alkaline environment and that the resultant alkyl ester is thereafter subjected to a fractionated precipitation by means of a surplus of urea in an alkanol,

and that this precipitation takes place by cooling the mixture to 0°C after having been heated to 55-90°C by a known method, whereafter the precipitated urea fatty acid alkyl ester adduct is separated and that the remainder which now mainly contains the essential  $\omega$ 3-fatty acid esters and the unsaponifiable portion is then extracted by a known method with a solvent for  $\omega$ 3-fatty acid alkyl esters and the unsaponifiable portion, whereafter the solvent after a preparatory cleansing of the extract with a water-soluble diluted acid is removed so that the resultant concentrate, together with its  $\omega$ 3-fatty acid alkyl esters and unsaponifiable portion is cooled for crystallization of cholesterol and other undefined unsaponifiable compounds.

4. Process for the production of a refined fish oil concentrate according to claim 3,  
c h a r a c t e r i z e d i n t h a t  
the fatty acid alkyl esters are treated with urea at a temperature preferably between 60-80°C, so that the urea fatty acid alkyl ester adduct in the main does not contain  $\omega$ 3-fatty acid compounds and unsaponifiable compounds.
5. Process for the production of a refined fish oil concentrate according to claim 4,  
c h a r a c t e r i z e d i n t h a t  
the solvent for  $\omega$ 3-fatty acid alkyl esters and the unsaponifiable is hexane.
6. Process for the production of a refined fish oil concentrate according to claim 4,  
c h a r a c t e r i z e d i n t h a t  
the hexane extract is cleansed with a diluted acid, preferably hydrochloric acid.

7. Process for the production of a refined fish oil concentrate according to claim 4, characterized in that the  $\omega$ 3-fatty acid alkyl ester concentrate after the solvent is removed, is cooled to a temperature not lower than  $-25^{\circ}\text{C}$ , whereby cholesterol is crystallized, and thereafter to  $-50^{\circ}\text{C}$  whereby the remaining portion of the unsaponifiable compounds precipitates.

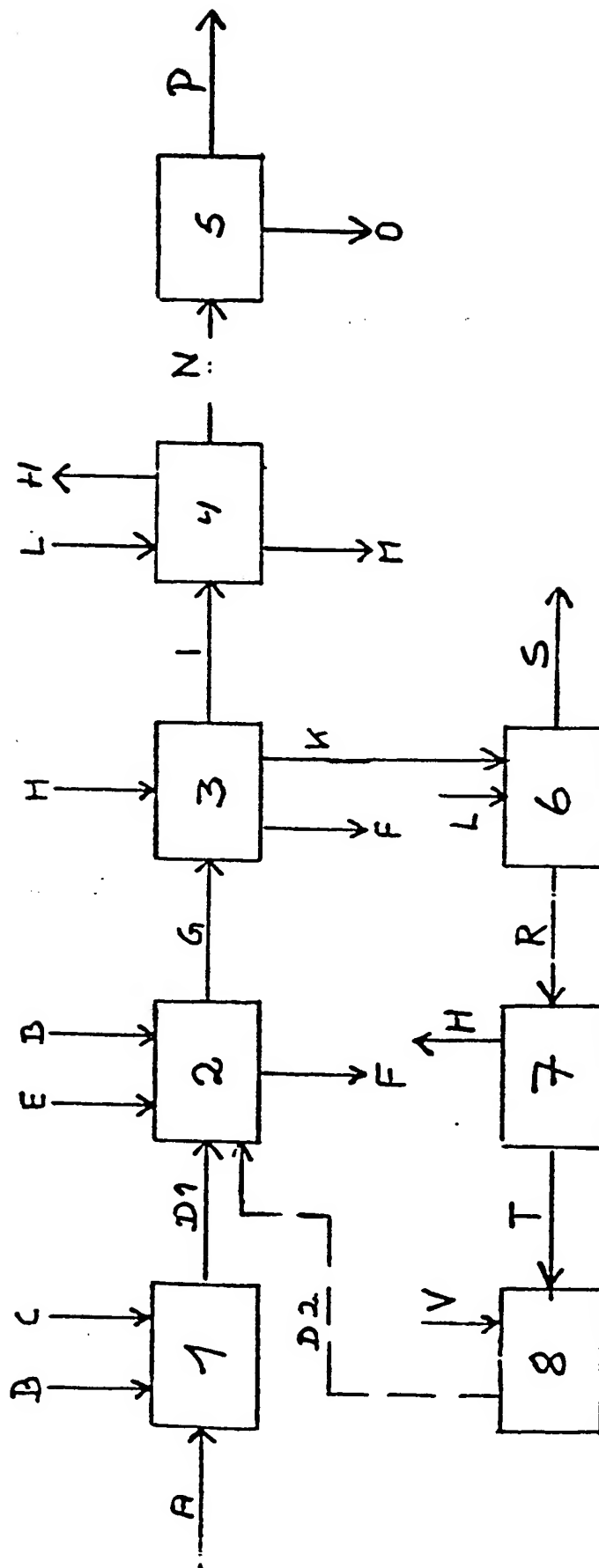


FIG. 1

# INTERNATIONAL SEARCH REPORT

International Application No PCT/N086/00077

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>4</sup> According to International Patent Classification (IPC) or to both National Classification and IPC <span style="float: right;">4</span> <div style="text-align: center; padding: 10px 0;">C 11 B 3/00, A 61 K 31/23</div>											
<b>II. FIELDS SEARCHED</b> <div style="text-align: center; padding: 5px 0;">Minimum Documentation Searched <sup>7</sup></div> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 25%; padding: 5px;">Classification System</th> <th style="padding: 5px;">Classification Symbols</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;">IPC 4</td> <td style="padding: 5px;">C 11 B 3/00, /02, 7/00, 13/00; C 11 C 1/00-/02, /08, 3/00, /04, /06-/10; A 61 K 31/23</td> </tr> <tr> <td style="padding: 5px;">US C1</td> <td style="padding: 5px;">260:410.7, 420-421; 426:417</td> </tr> </tbody> </table> <div style="text-align: center; padding: 5px 0;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup></div> <div style="padding: 10px 0;">SE, NO, DK, FI classes as above</div>			Classification System	Classification Symbols	IPC 4	C 11 B 3/00, /02, 7/00, 13/00; C 11 C 1/00-/02, /08, 3/00, /04, /06-/10; A 61 K 31/23	US C1	260:410.7, 420-421; 426:417			
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<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; padding: 5px;">Category <sup>9</sup></th> <th style="padding: 5px;">Citation of Document, <sup>11</sup> with Indication, where appropriate, of the relevant passages <sup>12</sup></th> <th style="width: 10%; padding: 5px;">Relevant to Claim No. <sup>13</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top; padding: 10px;">A</td> <td style="padding: 10px;">Patent abstract of Japan abstract of JP 86-07232.13 January 1986. 105(04)030124 chemabs patent 05030124.</td> <td style="text-align: center; vertical-align: top; padding: 10px;">1-2</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 10px;">A</td> <td style="padding: 10px;">EP, A1, 180 786 (ELVIRA PISTOLESI) 14 May 1986</td> <td style="text-align: center; vertical-align: top; padding: 10px;">1-2</td> </tr> </tbody> </table>			Category <sup>9</sup>	Citation of Document, <sup>11</sup> with Indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	A	Patent abstract of Japan abstract of JP 86-07232.13 January 1986. 105(04)030124 chemabs patent 05030124.	1-2	A	EP, A1, 180 786 (ELVIRA PISTOLESI) 14 May 1986	1-2
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A	EP, A1, 180 786 (ELVIRA PISTOLESI) 14 May 1986	1-2									
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>											
<b>IV. CERTIFICATION</b> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;">           Date of the Actual Completion of the International Search            1987-03-19         </td> <td style="width: 50%; padding: 5px;">           Date of Mailing of this International Search Report  <div style="text-align: center; padding: 10px 0;">1987-03-20</div> </td> </tr> <tr> <td style="padding: 5px;">           International Searching Authority  <div style="text-align: center; padding: 10px 0;">Swedish Patent Office</div> </td> <td style="padding: 5px;">           Signature of Authorized Officer  <div style="text-align: center; padding: 10px 0;">               Dagmar Järnman           </div> </td> </tr> </table>			Date of the Actual Completion of the International Search 1987-03-19	Date of Mailing of this International Search Report <div style="text-align: center; padding: 10px 0;">1987-03-20</div>	International Searching Authority <div style="text-align: center; padding: 10px 0;">Swedish Patent Office</div>	Signature of Authorized Officer <div style="text-align: center; padding: 10px 0;">               Dagmar Järnman           </div>					
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